

Epigenetic risk factors in PTSD and depression

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Epidemiological and clinical studies have shown that children exposed to adverse experiences are at increased risk for the development of depression, anxiety disorders, and posttraumatic stress disorder (PTSD). A history of child abuse and maltreatment increases the likelihood of being subsequently exposed to traumatic events or of developing PTSD as an adult. The brain is highly plastic during early life and encodes acquired information into lasting memories that normally subserve adaptation. Translational studies in rodents showed that enduring sensitization of neuronal and neuroendocrine circuits in response to early life adversity are likely risk factors of life time vulnerability to stress. Hereby, the hypothalamic-pituitary-adrenal (HPA) axis integrates cognitive, behavioral, and emotional responses to early-life stress and can be epigenetically programed during sensitive windows of development. Epigenetic mechanisms, comprising reciprocal regulation of chromatin structure and DNA methylation, are important to establish and maintain sustained, yet potentially reversible, changes in gene transcription. The relevance of these findings for the development of PTSD requires further studies in humans where experience-dependent epigenetic programming can additionally depend on genetic variation in the underlying substrates which may protect from or advance disease development. Overall, identification of early-life stress-associated epigenetic risk markers informing on previous stress history can help to advance early diagnosis, personalized prevention, and timely therapeutic interventions, thus reducing long-term social and health costs.

Keywords: PTSD, depression, early-life stress, HPA axis, epigenetic programming, epigenetic variation

INTRODUCTION

The overall burden of mental disorders – individual, societal, and economic – has been increasing in recent decades (1) and is greater than 10 years ago despite the availability of reasonably effective pharmacological and psychological interventions (2). Among mental disease posttraumatic stress disorder (PTSD) is a debilitating stress-related disease with prevalence rates amounting to 8%, and considerable higher rates among those living in high-violence areas and combat veterans (3–5). Originally thought of as a normative response to trauma, epidemiological studies showed that exposed subjects differed with respect to their later on risk for developing PTSD (6). This finding led to intense investigations to identify genetic and environmental factors associated with the onset, course, and treatment response of this disease. Overall, epidemiological and clinical studies have provided compelling evidence for a strong association between various forms of early life adversity, depression, and PTSD (Figure 1).

For this reason, we will refer the reader to the role of early life adversity for the development of depression whenever corresponding findings in PTSD are not available. This applies in particular to the role of experience-dependent epigenetic programming which is increasingly recognized as a mechanism in depression (7, 8). Moreover, given the central role of the hypothalamic-pituitary-adrenal (HPA) stress axis in response to early life adversity we will focus on its deregulation in both depression and PTSD. While PTSD and depression represent distinct entities, such a comparative approach can provide a conceptual framework for future studies in PTSD.

According to the National Comorbidity Survey Replication (9) early life adversity comprises interpersonal loss (parental death, parental divorce, and other separation from parents or caregivers), parental maladjustment (mental illness, substance abuse, criminality, and violence), maltreatment (physical abuse, sexual abuse, and neglect), life-threatening childhood physical illness in the respondent, and extreme childhood family economic adversity.

A landmark survey conducted at the Center for Disease Control showed a strong dose-response relationship between childhood adversities and mental health problems in adulthood (10). Patients suffering from major depression showed a fourfold increased risk for depression following multiple adverse exposures (11), a dose-response relationship between the severity of experienced childhood adversities and lifetime recurrent depression (12) and a twofold to fivefold increase in attempted suicide in up-growing children, adolescents, or later adults (13). These data corroborate with other representative surveys such as the National Comorbidity Survey (14), the Ontario Health Survey (15, 16), and the New Zealand Community Survey (17).

Similarly, individuals who were exposed to early life adversity are also more likely to develop PTSD (18, 19), to face re-exposure to trauma in adulthood, and to suffer from PTSD following trauma in adulthood (20–22) (Figure 1).

Hence, early life adversity is a powerful risk factor for mental diseases such as depression and PTSD and can predict a prolonged course and poorer response to treatment. The high incidence of child maltreatment represents an epidemic health problem and the

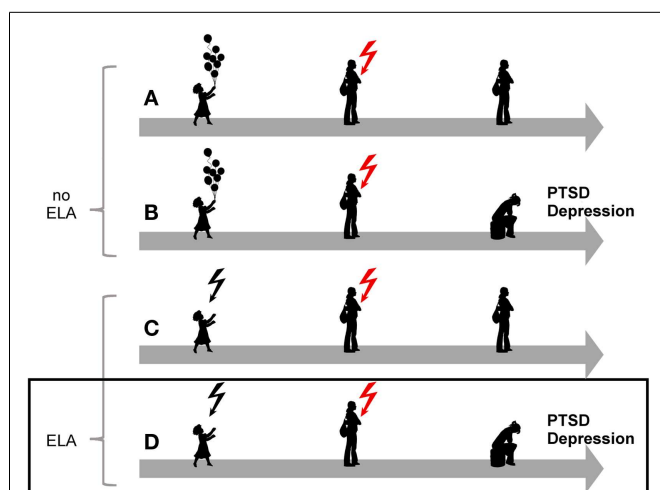


FIGURE 1 | Model for the role of early-life adversity for PTSD and depression.

In the absence of a history of early life adversity (ELA), adults can be resilient to disease upon exposure to severe trauma and stress (A) while others will develop PTSD or depression (B). Similarly, not all children exposed to early life adversity will develop disease upon anew exposure to trauma and stress (C). On the other hand, exposure to early life adversity in childhood can give rise to a vulnerable phenotype predisposing to disease upon anew exposure to trauma and stress (D).

long-term consequences of such trauma place a heavy burden on the healthcare system and society (23). According to the National Center of Child Abuse and Neglect approximately 3.4 million referrals, comprising alleged maltreatment of approximately 6.2 million children, were received across the US in 2011 (24). One-fifth of these children were found to be victims with disposition of substantiated (18.5%), indicated (1.0%), and alternative response victim (0.5%). All in all 676,569 victims of child abuse and neglect give rise to a unique victim rate of 9.1 victims per 1,000 children in the US population:

- more than 75% (78.5%) suffered neglect
- more than 15% (17.6%) suffered physical abuse
- less than 10% (9.1%) suffered sexual abuse
- more than four children (1,570 fatalities) died daily

These numbers recapitulated by and large prior findings (10, 25–28). Despite this compelling evidence for a link between early neglect, abuse, and later psychopathology (9, 29) knowledge about the molecular mechanisms underlying the long-term mental health consequences remains poor (30).

THE VULNERABLE BRAIN

Early brain development is a time of great opportunities and great vulnerabilities. The architecture of the developing brain is constructed through an ongoing process that begins before birth and extends into adulthood. Brain development and architecture are built from the bottom up with simple structures providing the scaffold for the formation of more advanced structures over time. Research in the field of neuroscience has provided compelling evidence for the high plasticity of the developing brain as

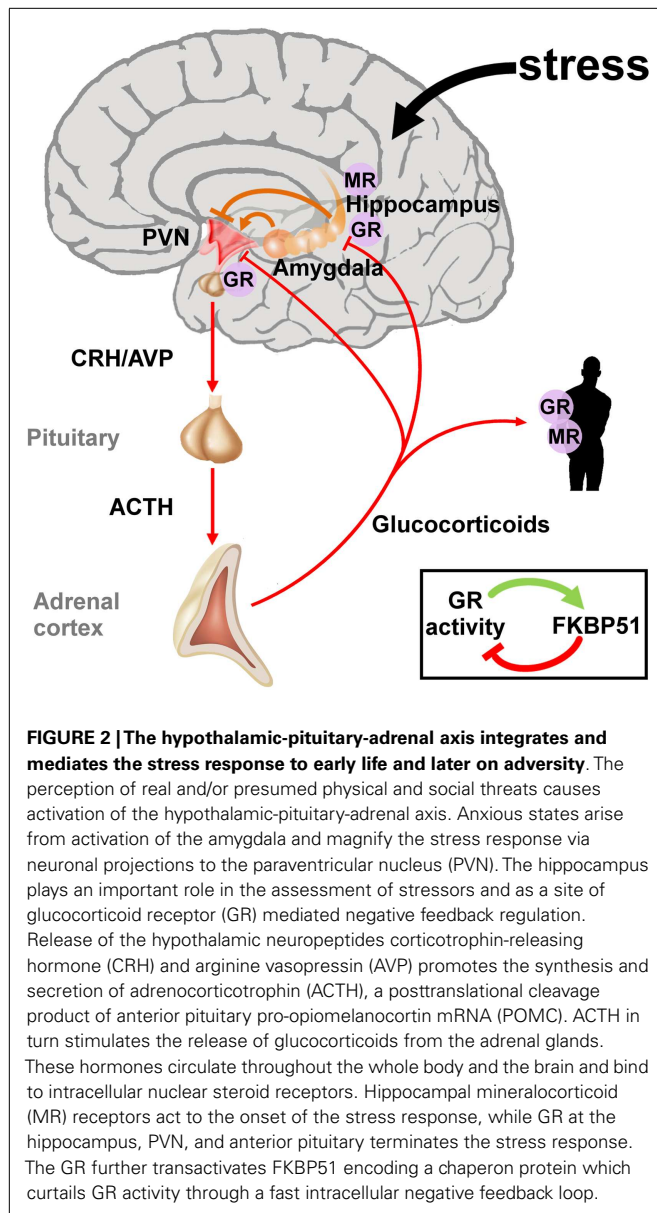
a function of experience which allows encoding of acquired information into lasting memories that normally subserve adaptation (31, 32). Sensitive periods refer to time windows during which developmental cues induce lasting programmable and organizational effects on neuronal substrates. Early adverse experiences in rodents and higher primates such as prenatal maternal stress, maternal separation, variable foraging demand, or naturally occurring low maternal care can lead to structural and functional changes in a connected network of brain regions implicated in neuroendocrine control, autonomic regulation, and vigilance (33–36). These neural changes converge on lifelong increased physiological and behavioral responses to subsequent stress (37). Ultimately, the enduring effects of early life adversity on the brain and its regulatory outflow systems, comprising the autonomic, endocrine, and immune systems, may lead to the development of a vulnerable phenotype with increased sensitivity to stress and risk for a range of somatic (38–40) and behavioral disorders (i.e., depression and PTSD) (9).

THE CENTRAL ROLE OF THE HPA AXIS

Early life adversity can cause lasting structural and regulatory adaptations in the neuroendocrine system predisposing to or protecting from stress-related diseases later in life (41–43). Initial studies on PTSD focused on the HPA axis due to its central position in the neuroendocrine stress response (Figure 2). The two neuropeptides corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) are secreted by the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN_h) and coordinate the behavioral and metabolic responses to stress. Binding to G-protein coupled receptors at the anterior pituitary gland induces co-operatively pro-opiomelanocortin (POMC) which is processed to adrenocorticotrophin (ACTH), opioid, and melanocortin peptides among others. Subsequently, ACTH stimulates the adrenal cortex to secrete cortisol (in humans) and corticosterone (in humans, rats, and mice). Corticosteroids activate ligand-gated glucocorticoid (GR) and mineralocorticoid (MR) receptors which are coexpressed in neurons of limbic structures. High levels of GR are additionally detected in the PVN_h and the anterior pituitary. The MR is thought to serve in the assessment and onset of the stress response whereas GR, requiring higher amounts of glucocorticoids for activation, terminates the stress reaction (44).

In contrast to the PVN_h, CRH neurons in the central nucleus of the amygdala project to the locus coeruleus and enhance the firing rate of its neurons resulting in increased noradrenaline release in the vast terminal fields of the ascending noradrenergic system (45). One of the principal noradrenergic targets are the CRH neurons of the PVN_h, which respond to increased activity in the nucleus tractus solitarius, the dorsal medullary nucleus, and the locus coeruleus (46). Experimental lesions of these regions result in a significant decrease in stress-induced PVN_h levels of noradrenaline, reduced plasma ACTH responses, and behavioral responses to stress (47, 48). In sum, CRH neurons in the PVN_h and the central nucleus of the amygdala jointly mediate behavioral and endocrine responses to stress.

Although commonly adaptive, sustained activation of these stress circuits results in impairments. Elevated central CRH activity is associated with symptoms of anxiety and depression. This



is most likely due to the CRH-induced stimulation of serotonergic and noradrenergic systems (49). Glucocorticoids and catecholamines enhance learning for information related to the stressor (50) whereas glucocorticoids impair attention and learning in relation to events not directly associated with the stressor (37). Additionally, glucocorticoids facilitate the behavioral effects of central Crh partly due to the upregulation of Crh in the central nucleus of the amygdala (51, 52).

LONG-TERM EFFECTS OF EARLY-LIFE ADVERSITY

In rodents and higher primates early-life stress lastingly influences the development of the central CRH systems underlying the expression of behavioral, emotional, autonomic, and endocrine responses to stress later in life (53, 54). Major depression frequently shows signs of a disinhibited HPA axis due to an increased parvocellular CRH expression which drives production and secretion of

pituitary ACTH and subsequently cortisol (Table 1). CRH over-expression reflects an impaired negative GR feedback regulation as evidenced by a reduced inhibition of cortisol secretion after application of the synthetic glucocorticoid dexamethasone (55) (Table 1).

Notably, depressed patients with a history of early child adversity were shown to differ in their neuroendocrine regulation. Although they shared signs of a hyperactive HPA axis, plasma cortisol is unaltered or reduced in part of these patients (Table 1). Moreover, their response to psychotherapy alone appeared superior to antidepressant therapy when compared to patients without a history of early child adversity (56).

Adult PTSD patients show a distinct neuroendocrine profile characterized by centrally elevated CRH, low plasma cortisol, and enhanced suppression of plasma cortisol and ACTH following the dexamethasone suppression test (Table 2). An increased responsiveness of both peripheral and central GR has been suggested as a plausible cause for hypocortisolemia (Table 2).

While hypocortisolemia in depressed patients is confined to those with a history of early life adversity (Table 1, right), PTSD patients are affected in either case (Table 2, left). This raises the question of whether hypocortisolemia precedes trauma exposure or whether it is a long-term consequence thereof promoting the manifestation of either depression or PTSD.

In this regard, longitudinal studies have shed some light on the development of HPA-axis deregulation in traumatized children. From an early age on, maltreatment, neglect, physical, and sexual abuse manifest with low levels of cortisol which persist into adulthood (Table 2, right). Furthermore, abused children display flattened diurnal cortisol levels (57) and increased cortisol suppression after administration of dexamethasone (58). These results corroborate the concept of an enhanced GR response and negative feedback function. However, sexually abused girls initially showed higher levels of cortisol after trauma exposure. Hypercortisolemia decreased, however, during growing up and cortisol remained low in young adults when compared to their unabused peers (59). A similar cortisol pattern has been detected in pediatric patients who experienced motor vehicle accidents and developed PTSD at 6 months. Initially, they had high levels of cortisol which passed over into hypocortisolemia at 6 months (60). Taken together, these findings suggest that trauma exposure associates with an acute stress response followed by hypocortisolemia and GR hyperresponsiveness in vulnerable subjects. This raises the important question of whether hypocortisolemia precedes clinical manifestation of PTSD and thus represents a potential marker for later on risk for illness (Table 2). In this respect, longitudinal studies identified low levels of cortisol as a risk factor to develop PTSD after trauma exposure (61–63).

In conclusion, neuroendocrine findings in PTSD and individuals exposed to early life adversity indicate that hypocortisolemia *per se* does not result in PTSD but seems to increase the risk to develop disease following additional trauma exposure. The cellular and molecular mechanisms causing hypocortisolemia due to enduring deregulation of the HPA axis and how they interact with later on trauma to manifest as PTSD are presently largely unknown.

Table 1 | Neuroendocrine status in depressed patients without and with a history of early life adversity.

	MD	Reference	MD + ELA	Reference
CRH	↑	Nemeroff et al. (139)	↑	Carpenter et al. (140)
	↑	Raadsheer et al. (141)		
	↑	Wang et al. (142)		
Cortisol	↑	Sachar et al. (143)	↓	Shea et al. (144)
	↑	Holsboer et al. (145)	↓	Heim et al. (146)
	↑	Holsboer et al. (147)	↑	Gerra et al. (148)
	↑	Wingenfeld et al. (149)	=	Heim et al. (150)
	↑	Carvalho Fernando et al. (151)	↑	Power et al. (152)
	↑	Hinkelmann et al. (153)		
	↑	Messlerli-Bürgy et al. (154)		
	↑	Yilmaz et al. (155)		
DST	Cortisol ↑	Carroll et al. (156)	ACTH ↓ cortisol ↓	Newport et al. (157)
	ACTH ↑ cortisol ↑	Modell et al. (158)		
	Cortisol ↑	Carvalho Fernando et al. (151)		
CST	ACTH ↑	Holsboer et al. (147)	ACTH ↓ cortisol ↓	Heim et al. (146)
	ACTH ↓	Heim et al. (146)	Cortisol ↑	Heim et al. (150)

MD, major depression; ELA, early life adversity; DST, dexamethasone suppression test; CST, corticotrophin-releasing hormone stimulation test; ACTH, adrenocorticotrophin hormone.

In the following parts, we will explore the possibility of epigenetic mechanisms to encode traumatic experiences. We will further argue that insight from experience-dependent epigenetic programming by early-life adversity in depression can serve as guidance to advance translational studies in PTSD.

A GUIDE TO DNA METHYLATION

The epigenetic landscape has unfolded at multiple layers involving DNA methylation, histone modifications, non-coding RNA, and nucleosome positioning; along with DNA sequence. For the purpose of this review we will consider only the former two and refer the interested reader to recent reviews (64–66).

As a stable, though potentially reversible, repressive mark, DNA methylation is considered to represent an important player in epigenetic control of transcription (67). DNA methylation is carried out by a family of DNA methyltransferases (DNMTs) comprising DNMT1, DNMT3A, DNMT3B, and DNMT3L. DNMT1 primarily methylates hemimethylated DNA *in vitro* and is recruited to replication foci during S phase, while DNMT3A and DNMT3B preferentially recognize unmethylated CpG dinucleotides and regulate *de novo* methylation during development.

Specific histone modifications and DNA methylation reciprocally influence each other in deposition (Figure 3). Mechanistically, components of the histone methylation system associate physically with one or more DNMTs. For example, trimethylation of H3K9, H3K27, and H4K20 emerged as a prerequisite for subsequent DNA methylation. The methyltransferases SUV39H1/2 and EZH2 catalyzing H3K9 and H3K27 methylation, respectively, bind directly to DNMT1, DNMT3A, or DNMT3B and facilitate their recruitment to target loci (68, 69). Similarly, the recruitment of HP1 (heterochromatin protein 1) to constitutive heterochromatin results from SUV39H1/2-mediated trimethylation of

H3K9 while euchromatin binding depends on dimethylation catalyzed by the histone methyltransferase G9A (70). Once bound, HP1 can directly interact with DNMT3A to guide DNA methylation (71). Conversely, histone methylation can also interfere with DNA methylation. DNMT3L, lacking catalytic activity, specifically recognizes the extreme amino terminus of the core histone H3 in a methylation sensitive manner. Methylation of H3K4 but not of other residues blocks interaction with DNMT3L and the subsequent recruitment of DNMT3A2 (72).

Taken together, histone methylation can both facilitate and impair the recruitment of DNMTs and intermediary factors in a context dependent manner to impose changes in DNA methylation and the long-term control of gene activity (Figure 3).

The globally methylated, CpG poor genomic landscape is punctuated by CpG islands (CGIs). Approximately 70% of all annotated gene promoters are associated with a CGI that are typically free of DNA methylation (73). In mammals tissue- and cell type-specific DNA methylation is detected in a small percentage of 5' CGI promoters whereas most DNA methylation occurs in intra- or inter-genic regions which unexpectedly correlates with increased rather than decreased transcription (74–76) or alternatively with elective promoter usage (77).

Active DNA demethylation in mammals remains presently subject of intense investigation as cytosine deamination, oxidation, and base excision repair enzymes have been suggested in a variety of combinations (78).

A second, more recently discovered mechanism implicates the actions of ten eleven translocation (TET) proteins which convert 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) by an oxygen-, and α -ketoglutarate-dependent mechanism, then to 5-formylcytosine and hereafter to 5-carboxycytosine (79). This modified residue is excised by glycosylases to be replaced by

Table 2 | Neuroendocrine status in PTSD patients without and with a history of early life adversity and in healthy controls exposed to early life adversity.

	PTSD	Reference	ELA	Reference
CRH	↑ ↑ ↑	Bremner et al. (159) Baker et al. (161) de Kloet et al. (162)	↑	Lee et al. (160)
Cortisol	↑→ ↓ <i>Ch</i> ↓ <i>ELA</i> ↓ <i>ELA</i> ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ <i>RF</i> ↓ <i>RF</i> ↓ <i>RF</i>	Pervanidou et al. (60) Bremner et al. (164) Brand et al. (166) Yehuda et al. (168) Boscarino (170) Yehuda et al. (172) Thaller et al. (174) Rohleder et al. (175) Bierer et al. (176) Brand et al. (177) Wingenfeld et al. (149) Resnick et al. (61) McFarlane et al. (62) Delahanty et al. (63)	↓ <i>Ch</i> ↓ <i>Ch</i> ↓ <i>Ch</i> ↓ <i>Ch</i> ↓ <i>Ch</i> ↓ <i>Ch</i> ≈ <i>Ch</i> ↑ <i>Ch</i> → ↓ ↓ ↓ ↓ ↓ ≈ <i>Ad</i> ≈ <i>Ad</i>	Carlson and Earls (163) King et al. (165) Kliewer (167) Bevans et al. (169) Badanes et al. (171) Hauser et al. (173) Bruce et al. (57) Trickett et al. (59) Resnick et al. (61) Brewer-Smyth and Burgess (178) Flory et al. (179) Power et al. (152) Weissbecker et al. (180) van der Vegt et al. (181)
GR-r	↑ ↑ ↑	Yehuda et al. (182) Yehuda et al. (183) Yehuda et al. (184)	↑	Heim et al. (146)
DST	Cortisol ↓ ACTH ↓ <i>ELA</i> ACTH ↓ cortisol ↓ ACTH ↓	Yehuda et al. (183) Duval et al. (185) Yehuda et al. (187) Ströhle et al. (189)	Cortisol ↓ <i>Ch</i> Cortisol ↓ Cortisol ↓	Goenjian et al. (58) Stein et al. (186) Heim et al. (188)
CST	ACTH ↓ cortisol ↓	Ströhle et al. (189)	Cortisol ↑ Cortisol ↓ ACTH ↑	Heim et al. (188) Carpenter et al. (190) Heim et al. (146)

PTSD, posttraumatic stress disorder; ELA, early life adversity; GR-r, glucocorticoid receptor reactivity; DST, dexamethasone suppression test; CST, corticotrophin-releasing hormone stimulation test; ACTH, adrenocorticotrophin hormone. Indices are; RF, risk factor for PTSD; Ch, children; ≈Ch or ≈Ad, flattened diurnal cortisol in children or adults.

cytosine via the base repair system (80). Interestingly, hydroxymethylation can be selectively recognized by DNA-binding proteins raising the prospect that it serves a biological function on its own (81). For example, Mbd3 preferentially binds to 5-hmC relative to 5-methylcytosine to confer gene repression (82).

In sum, DNA methylation occurs at different gene regulatory regions controlling transcription, alternative promoter usage, and splicing. Methylation of CpG residues is a stable though potentially reversible mark catalyzed by enzymatic conversion.

AN EPIGENETIC ARCHIVE

The “DNA ticketing theory of memory” was proposed some 40 years ago by Griffith and Mahler to account for the extraordinary persistence of memory (83). Given that “nerve cells do not normally divide in adult life and their DNA is generally considered to be metabolically stable” they hypothesized that “the physical basis of memory could lie in the enzymatic modification of the DNA of nerve cells” whereby “the modification consists of methylation (or demethylation).” This concept has been reviewed

by Holliday who proposed that “the initial signal which is to be memorized, switches the DNA from a modified to an unmodified state, or vice versa;” thereby, “demethylation is a more likely possibility since from existing evidence this may activate a gene” (84). This hypothesis has been largely ignored because DNA methylation was originally thought of as part of a stable, epigenetic cellular memory system that controls gene silencing via chromatin structure. Hence, postmitotic cells were considered to be refractory to any changes in DNA methylation. Recent reports suggest, however, that DNA methylation is also involved in controlling the dynamics and plasticity of gene regulation, particularly during differentiation (85). Moreover, DNA methylation in postmitotic neurons can respond to social experiences and encode lasting changes in gene expression (86). In this regard, experience-dependent DNA memories can be described as the sequential process of a social and/or physical event registered by sensory and cognitive brain areas. The subsequent activation of intracellular signaling pathways, coupled to the epigenetic machinery, and ultimately its recruitment to specific gene loci, enables to erase, establish, and maintain epigenetic

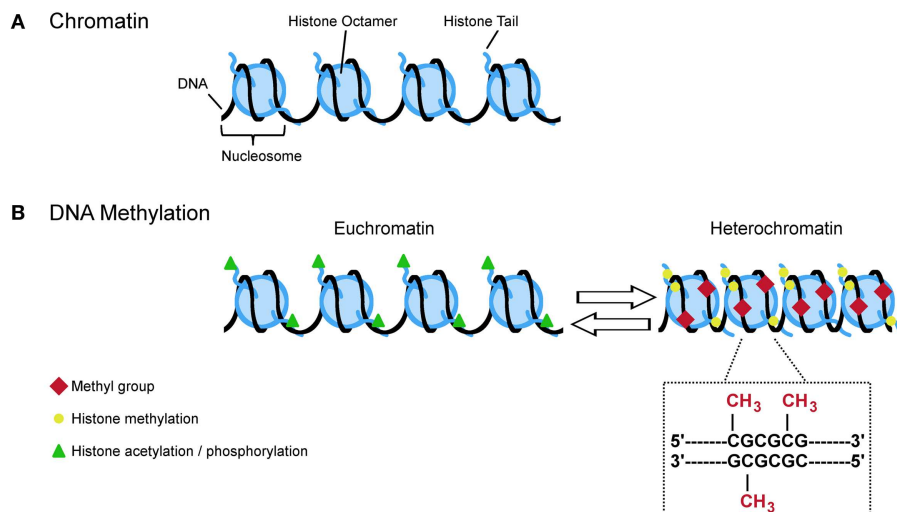


FIGURE 3 | A (simplified) guide to DNA methylation. (A) Approximate 147 bp of DNA are wrapped around the nucleosome which is made up by the core histones H2A, H2B, H3, and H4. The free ends of the histone tails serve as substrate for posttranslational modifications (e.g., acetylation, phosphorylation, and methylation) that influence the configuration of chromatin. Opened states (euchromatin) allow transcription while closed states (heterochromatin) restrict the transcriptional machinery. **(B)** Euchromatin is characterized by acetylation and phosphorylation (green

triangles) whereas methylation (yellow circles) is more often found at heterochromatin. Specific histone modifications and DNA methylation reciprocally influence each other in deposition. For example, histone methylation at H3K9, H3K27, and H4K20 promotes DNA methylation at CpG dinucleotides. This covalent modification refers to the transfer of methyl group to cytosine residues at gene regulatory regions. Hypermethylation typically links to lasting transcriptional repression while hypomethylation favors gene expression.

marks. Admittedly, not all examples of early-life stress-dependent changes in DNA methylation can satisfy these criteria (7).

For the purpose of this review, we will focus on those genes of the HPA axis known to be lastingly deregulated in both depression and PTSD and ask whether epigenetic programming contributes to these processes. Experience-dependent programming of the HPA axis has been intensively studied in rodents and examples given below serve to illustrate the overarching concept without attempting to provide a comprehensive survey of this field. In considering epigenetic programming of key regulators of the HPA axis, a developmental perspective (i.e., embryonic, prenatal, postnatal, and adult stages) is adopted whenever possible to illustrate that the brain is susceptible to epigenetic programming across the entire life span.

EXPERIENCE-DEPENDENT PROGRAMING OF CRH

Parvocellular hypothalamic CRH-expressing neurons participate both in the peripheral and central stress systems by governing secretion of ACTH from the pituitary contributing to the peripheral, neuroendocrine stress response, and by modulating stress-related behavior including anxiety as well as learning and memory. The CRH peptide is additionally detected in neocortex and in limbic regions including the central nucleus of the amygdala, the dorsal and ventral part of the bed nucleus of the stria terminalis, and the hippocampus. Further sites comprise the locus coeruleus, dorsal and median raphe, periaqueductal gray, nucleus of the solitary tract, and cerebellar complex. For the purpose of this review, we will focus in the following section largely on stress-dependent programming of *Crh* in the PVN_h.

Early-life experience can evoke lasting changes in *Crh* expression levels in the PVN_h as evidenced by several paradigms

comprising onetime or repeated separation from the mother for up to 24 h, manipulation of maternal behavior by “handling” and limiting nesting materials for the dam during the first weeks of life. In this respect, maternal separation for 24 h has been documented to either not influence (87) or reduce basal *Crh* gene expression in rat (88) and mice PVN_h (89). Of note, prolonged maternal separation for 8 h leads to desensitization of the HPA axis with reduced corticosterone after replication of prolonged maternal separation (90, 91). In response to acute stress, maternal deprivation leads, however, to higher transcription of the *Crh* gene and rapid secretion of ACTH and glucocorticoids (87, 92–94).

Enhanced maternal care due to natural variation (95, 96) reduces *Crh* expression in the PVN_h in the adult offspring, curtails hormonal responses to stress, and enhances hippocampal GR levels. Similarly, daily brief (15 min) separations from the mother during postnatal week 1 up to 3 promotes an adult phenotype characterized by a sensitization of the HPA axis with an attenuated stress response (33, 97) associated with reduced basal expression of *Crh* in the PVN_h and increased hippocampal expression of the GR (98, 99). Hereby, the reduction of *Crh* expression in the PVN_h precedes further changes at different levels of the HPA axis compatible with the idea that *Crh* mediates handling-evoked maternal care to adaptation of the HPA axis (99, 100).

Sustained early-life stress can also be generated by limiting the amount of nesting material which creates an enduring stressor for the dam. This leads to fragmented maternal care and imposes an additional stressor on the pups (101, 102). By the end of 1 week of postnatal stress (P9), *Crh* mRNA expression in the PVN_h of the early-life stress group is significantly reduced compared to undisturbed controls (102). Reduced *Crh* expression may reflect

altered glucocorticoid negative feedback and/or increased *Crh* release concomitant with a failure of acute stress-induced *Crh* production.

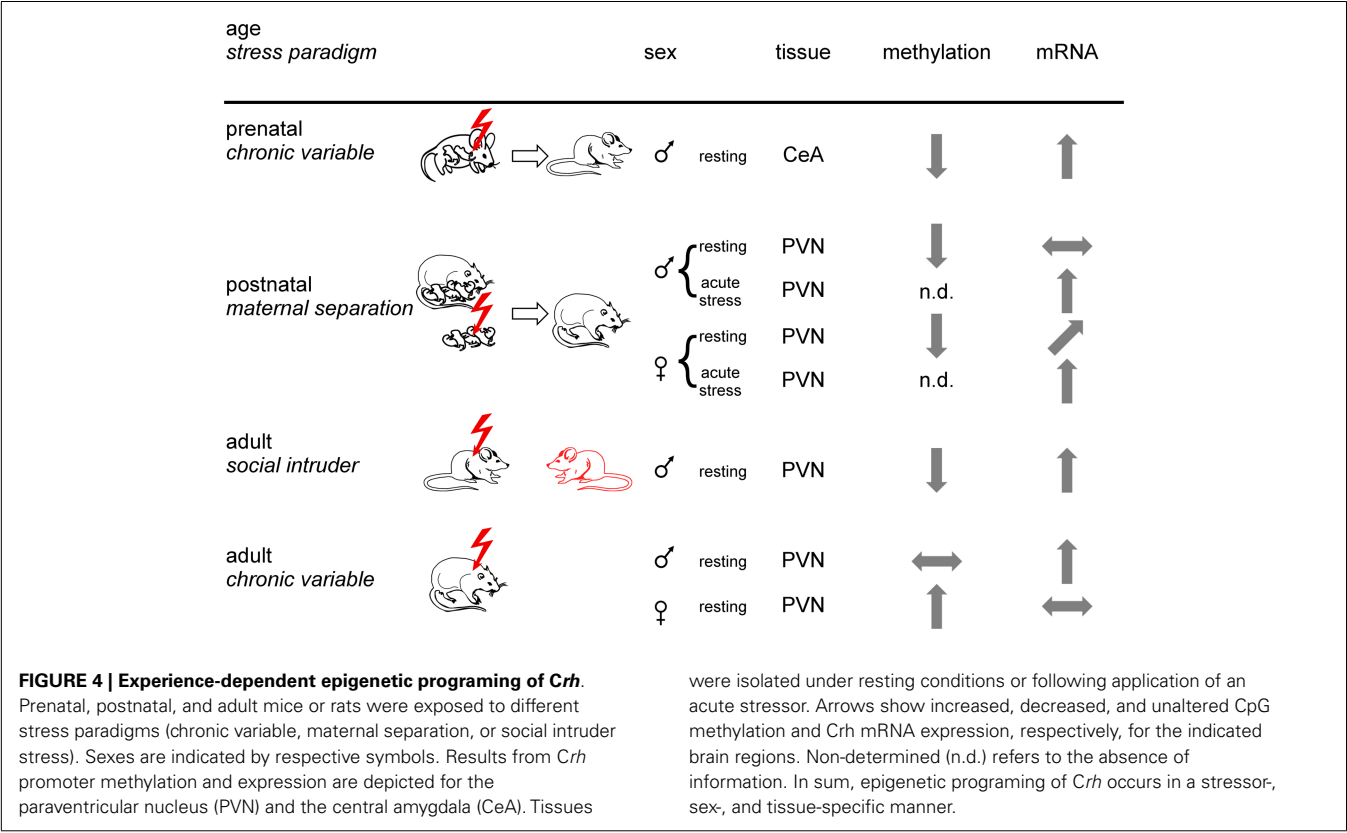
Collectively, these exemplary studies in rodents illustrate that early trauma and stress can cause sustained changes in *Crh* expression which critically depend on the developmental stage of the limbic-HPA axis. Are then any of these changes in *Crh* expression related to epigenetic mechanisms such as DNA methylation?

EPIGENETIC PROGRAMING OF *Crh*

The fetus grows up in the womb protected by the placental barrier which shields from any adversity that might arise in the maternal environment. Severe stressors and strains can, however, compromise the placental barrier and expose the developing fetal brain to maternally derived substances, such as cytokines or stress hormones. The latter can trigger increased vulnerability to depression, anxiety, schizophrenia, and autism (103). In this respect, male but not female mice offspring exposed to chronic variable stress early in gestation (embryonic day 1–7) displayed impaired behavioral stress responsivity, anhedonia, and an increased sensitivity to treatment with a selective serotonin reuptake inhibitor (104). Increased *Crh* expression in the amygdala is associated with decreased promoter methylation (Figure 4), while decreased GR expression in the dorsal hippocampus correlated with increased methylation at the NGFI-A binding site of exon 1₇ (see below). Notably, the fetal brain was unformed at the time the stressor was applied to the mother indicating that sex-specific changes in fetal development and long-term adaptation of the HPA axis might

be mediated through effects on the developing placenta. In this regard, male control placentas showed lower *Dnmt1* expression compared to females. Moreover, increases in placental *Dnmt1* in response to prenatal stress were largely confined to females. How increased *Dnmt1* expression might counteract prenatal stress-dependent perturbations in placental gene expression remains presently unknown.

In a postnatal study, rats exposed to early-life stress (maternal separation) were studied for HPA-axis responses to acute restraint stress and *Crh* promoter methylation in the PVN_h nucleus and the central nucleus of the amygdala (105). Despite slightly lower plasma ACTH, plasma corticosterone levels in female rats subjected to early-life stress were significantly higher in basal conditions and after exposure to acute restraint stress. In males, early-life stress did not affect basal plasma corticosterone levels, but in females the increases after restraint were significantly higher in early-life stressed males than in controls. In accord with these findings, *Crh* mRNA expression in the PVN_h was increased under resting and acute stress conditions in females while increases in males occurred only under acute stress conditions (Figure 4). Moreover, *Crh* expression in the central amygdala was unaffected in either condition in both sexes. Early-life stress associated with hypomethylation of the *Crh* promoter in the PVN_h in either sex and mapped to two CpG residues localized next to and at the dyad symmetry axis of a cyclic AMP responsive element (CRE). Methylation of the latter CpG residue impaired DNA binding of the activated form of the CRE binding protein (p-CREB) compatible with the idea that early-life stressed induced hypomethylation



facilitates CREB binding and subsequently basal and activated *Crh* transcription.

Exposure to social defeat over 10 consecutive days imposes sustained social stress on adult male mice resulting in anhedonia and social avoidance. This well-known paradigm associated with demethylation at the proximal *Crh* promoter (106). As a result, *Crh* mRNA expression in the PVN_h was significantly increased (Figure 4). Interestingly, *Crh* demethylation was confined to males displaying signs of stress while those being unaffected escaped demethylation and *Crh* overexpression. Given that genetically homogenous mice were housed and tested under standardized operating procedures this differential response suggests that subtle differences in the previous life histories can modify the outcome from exposure to stress. Application of imipramine over 3 weeks, a clinically relevant time period, improved the social avoidance behavior and reversed changes in *Crh* promoter methylation and gene expression. *Crh* demethylation was preceded by decreases in *Dnmt3b* and *Hdac2* expression, while *Gadd45b* expression was temporarily increased. In this regard, *Gadd45b* has been shown to subserve demethylation by facilitating recruitment of the DNA repair machinery (107, 108).

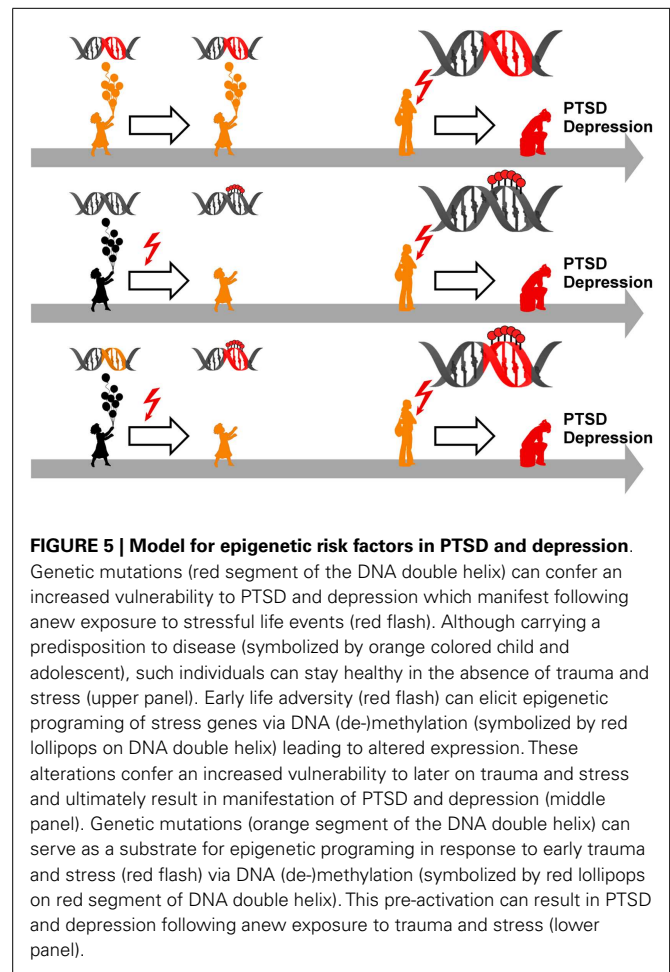
In a further study, adult male and female rats were exposed to chronic variable stress after which *Crh* expression and promoter methylation was measured in the PVN_h, the bed nucleus of the stria terminalis and the central amygdala (109). Chronic variable stress produced *Crh* promoter hypermethylation at specific CpG dinucleotides in all tissues examined in females while the effects in males were confined to the stria terminalis and the central amygdala. In the PVN_h, chronic variable stress increased *Crh* expression in the males (in the absence of changes in methylation), while the *Crh* peptide decreased in females most likely due to increased promoter methylation (Figure 4). This study firstly evidenced sex-specific epigenetic programming of *Crh* and illustrates the importance of sex differences in brain epigenetics (110). The functional implications of decreased *Crh* expression in females in the presence of elevated corticosterone levels requires, however, further investigations.

Together, these studies show that epigenetic programming of *Crh* can occur in a stressor-, tissue-, and sex-specific manner. Moreover, differences in the previous life history might protect from epigenetic programming. Subsequent variations in DNA methylation at the *Crh* gene can serve to distinguish the transcriptional response to later stress-related stimuli. Experience-dependent programming of gene expression potential can thus confer an increased risk to anew stress exposure and the manifestation of stress-related diseases such as depression and PTSD (Figure 5).

EXPERIENCE-DEPENDENT PROGRAMING OF *Avp*

Newborn rats exposed to repeated brief maternal separation and handling (PND 1–10) showed as adults reduced social investigative interactions and increased aggressive behavior with a higher frequency of attacks in the social interaction test. The latter behavior was detected only in males which displayed an increased number of *Avp*-positive magnocellular neurons in the PVN (111).

A related phenotype was detected following maternal separation in mice (112). While both sexes displayed increased anxiety-related behavior (reduced time spent on open arms in the elevated



plus-maze and reduced exploration time of novel objects) this alteration associated with sex-specific differences in *Avp* expression. In this respect male but not female mice showed increases in *Avp* immunoreactivity in magnocellular neurons of the PVN and the lateral hypothalamus.

Sex differences in response to early-life adversity are not limited to *Avp* but extend to the receptor level. Adult rats that were reared by high licking and grooming mothers showed increased *Avp* V1a receptor binding in the central nucleus of the amygdala (113).

A recent study in human strengthens the importance of sex differences in *AVP* expression and suggests possible therapeutic consequences (114). PTSD is associated with problems in intimate relationships, partly due to impaired social cognition. Attention to partner expressions of anger was investigated as an indicator of distress and need for affiliative behaviors to repair the relationship bond. *AVP* administration enhanced men's attentional engagement with their partners' expressions of anger and alleviated the negative impact of PTSD on this social cognitive process. Moreover, men's morning urinary *AVP* levels were negatively correlated with their PTSD severity. In contrast, no such effects were detected among women or for attention to unfamiliar men's or women's anger expressions.

Collectively, early-life adversity preferentially programs the expression of hypothalamic *Avp* and its receptor in male rodents. Moreover, deficits in social cognition in male PTSD patients are improved following AVP administration.

EPIGENETIC PROGRAMING OF *Avp*

Maternal separation (3 h per day from postnatal day P 1–10) has been used to study early-life stress in male mice. Consistent with previous studies, adult mice displayed a hyperactive HPA axis characterized by corticosterone hypersecretion under resting conditions and following application of an acute stressor. These findings associated with enhanced immobility in the forced swim test and memory deficits in an inhibitory avoidance task (115).

Whereas hypothalamic *Crh* mRNA expression was not affected by early-life stress, the paradigm resulted in a sustained upregulation of *Avp*. This response was confined to the PVN_h coordinating the stress response whereas *Avp* expression in the supraoptic hypothalamic nucleus which controls fluid homeostasis remained unaffected. Increased *Avp* expression correlated with reduced levels of DNA methylation at multiple CpG residues at a downstream enhancer region which serves to fine-tune gene expression. Hypomethylation evolved gradually in response to maternal separation to reach a maximum at 6 weeks. Thereafter, changes in DNA methylation declined slowly but were still detectable after 1 year (115).

Hypomethylation localized to high affinity DNA-binding sites for the methyl-CpG-binding protein *Mecp2*. This epigenetic reader serves as a scaffold for the assembly of DNMTs and histone deacetylases which can rewrite epigenetic marks to induce gene silencing (86, 116). Hypomethylation in 6-week-old early-life stress treated mice reduced *Mecp2* binding at the *Avp* enhancer and consequently promoted increased gene expression.

Early-life stress treated mice showed, however, no signs of hypomethylation directly after termination of the stressor (postnatal day 10) although *Avp* expression was robustly increased. This finding indicated that stress signals unrelated to DNA methylation appear to control binding of *Mecp2* at earlier stages. In support of this concept, depolarization-dependent Ca^{2+} influx and activation of calmodulin kinases has been shown to cause *Mecp2* phosphorylation. This event impairs *Mecp2* DNA binding and derepresses target genes (115). In accord with this hypothesis, early-life stress treated mice showed increased *Mecp2* phosphorylation in parvocellular *Avp*-expressing neurons at postnatal day 10.

Taken together, these results suggest a stepwise mode for epigenetic programing of *Avp*. Initially, early-life stress leads to phosphorylation of the epigenetic reader *Mecp2*. This modification favors dissociation from the *Avp* enhancer and promotes increased expression. Moreover, due the absence of *Mecp2*, epigenetic writers like DNMTs and histone deacetylases lose their docking sites and will fall short to maintain DNA methylation. As a result *Avp* hypomethylation will gradually evolve and leave a persistent memory trace of the early-stress event encoding an altered stress regulation.

This stepwise mode of epigenetic programing of *Avp* in response to early trauma involves the transition from stress-induced posttranslational modifications (so called soft-wiring) to stable DNA modifications (so called hard wiring). Although there

are so far no related studies in humans, we want to point out that changes following from exposure to early life adversity appear initially reversible. They might, however, solidify over time or upon re-exposure to stress. In this respect, early interventions such as improvements in parenting and the social environment might delay or protect individuals exposed to early trauma to develop disease at later stages.

EXPERIENCE-DEPENDENT PROGRAMING OF GR

Experience-dependent programing of the HPA axis also applies to negative feedback regulators like the GR. Enhanced maternal care during the first 10 days of life (95) and daily short (15 min) periods of maternal separation during the first postnatal week (98, 99) increase hippocampal GR expression in adult rodents. This event leads to decreased hypothalamic *Crh* expression and an attenuated response upon acute stress exposure over life span (117, 118).

On the other hand, extended periods of maternal separation (up to 4.5 h per day) change the direction of GR expression later in life and manifest with reduced expression of hippocampal GR in rodents. Consequently, negative feedback regulation of the HPA axis is impaired as evidenced by elevated levels of ACTH and corticosterone in adulthood (98). These early life dependent alterations in GR expression can be reversed by housing up-growing animals under an enriched environment which normalizes GR expression, behavioral, and memory performance (119).

EPIGENETIC PROGRAMING OF GR

The molecular foundations of epigenetic programing of the GR in response to early life care have been discovered by Meaney and Szyf in a series of elegant studies (120) [reviewed in (42, 121)]. Briefly, natural variations in maternal care can stimulate to different degree serotonin turnover in the hippocampus of 6-day-old rat pups, where GR expression is site-specifically increased. Following binding to its receptor, serotonin activates via protein kinase A the expression of the immediate early gene *NGFI-A* encoding a zinc finger transcription factor. *NGFI-A* protein binds in turn to its recognition site at exon 17 of the proximal GR promoter to enhance transcription.

How do these events establish a lasting record of maternal care? Multiple untranslated first exons of the proximal GR promoter are transcribed as a result of the associated promoter activity and are spliced on the common second exon to give rise to the same GR protein. The major part of the proximal GR promoter, including most alternative exons and the hippocampus-specific exon 17, are contained within a CGI. As alluded above, CGIs can be subject to DNA methylation and serve to control gene expression potential. In this respect the offspring from high-care taking mothers showed decreased CpG methylation at the *NGFI-A* binding site when compared to offspring of the same age from low-care taking mothers. These differences developed in the first postnatal week concurrent with differences in maternal care and its effect on *NGFI-A* expression (122). Differences in maternal care disappeared after the first postnatal week and consequently adult rats did not diverge anymore in hippocampal *NGFI-A* expression. Maintained hypomethylation left, however, an enduring memory trace of the postnatal environment and underpinned increased GR expression restraining HPA-axis activity in response to future stressors.

Epigenetic programming of *GR* occurs also in adult mice. Chronic and acute stress during adulthood induces changes in the methylation level of the *GR* promoter at exon 1 γ in the pituitary and adrenal gland whereas brain tissues remained unaffected (123). This result corroborates above findings from *Crh* and suggests that epigenetic programming is tissue-specific dependent on developmental stage.

The hypothesis that early life adversity in humans induces similarly epigenetic programming of hippocampal *GR* expression has been addressed by postmortem brain analysis from suicide victims (124). The documented histories of childhood adversities included severe sexual or physical abuse and neglect. Interestingly, total *GR* and exon 1F (the human homolog of rat exon 1 γ) expression in the hippocampus was reduced in suicide victims with a history of abuse, but not in those without such a history or in control subjects. These results indicate that *GR* expression associated with early life adversity rather than with circumstances of life leading the way to suicide. These results agree with above findings from rodents that epigenetic programming of *GR* depends on the developmental context. Together, these studies in human and rat support the concept of a DNA-based memory that underpins the lasting effects of early life adversity.

Does then prenatal adversity also cause epigenetic programming of *GR*? Children whose mothers' were exposed to enduring stress during pregnancy (i.e., depression, anxiety, death of a relative, or marital discord) suffer from increased rates of psychological and behavioral disorders as adults (103). Hereby, the respective offspring frequently shows signs of HPA-axis deregulation similar to those detected in their depressed mothers (125). In support of above consideration, maternal depression in the third trimester led to an increased neonatal methylation of the presumed NGFI-A DNA-binding site situated at exon 1F in cord blood cells. Additionally, newborn methylation at nucleotide residue CpG3 associated with an enhanced cortisol response to an experimental stressor at 3 months of age (126). These data suggest that gestational depression can elicit epigenetic programming of peripheral and possibly central *GR* expression in neonates which might result in altered HPA-axis responsiveness in small children.

How long does epigenetic programming of neonate *GR* in response to maternal depression last? In a further study exon 1F methylation was measured in a group of children in the range from 10 to 19 years and in their respective mothers. Retrospective psychological evaluations were used to identify those mothers who had been exposed to physical or psychological abuse before, during, or after pregnancy. Exon 1F methylation was increased in adolescent children whose mothers' had experienced intimate partner violence during pregnancy (127). In contrast, adolescent exon 1F methylation was unaffected in case of prenatal or postnatal maternal abuse pointing to the critical role of gestational stress in epigenetic programming of fetal *GR*. Moreover, none of the respective mothers presented with altered exon 1F methylation in peripheral blood mononuclear cells (PBMC) suggesting that epigenetic programming of *GR* is confined to few sensitive time windows during development.

In further support of this idea, individuals suffering from major depression or borderline personality disorders exhibit increased exon 1F methylation in PBMC. Changes in DNA methylation were

more prominent in the latter group and correlated in either with a history of child abuse, its severity, and the exposure to multiple types of maltreatment (128). Interestingly, healthy adults with a history of childhood adversity (maltreatment, poor quality parenting, loss of parents) show as well increased CpG3 methylation at exon 1F in PMBC and an attenuated cortisol response to the dexamethasone/CRH test (129). This finding corroborates that variation in parenting experiences in humans can bring about epigenetic programming of *GR* and HPA-axis deregulation without clinical manifestation. In this respect, additional stressors appear necessary to give rise to diseases such as depression and PTSD (Figure 5). Collectively, changes in exon 1F methylation seem to fulfill the criteria of an epigenetic risk marker to identify persons at future risk. Follow-up studies are needed to test this hypothesis and to explore exon 1F methylation as a potential biomarker for treatment response and relapse upon disease's manifestation.

GENE-ENVIRONMENT INTERACTIONS IN PTSD

Since the days of Garrod (130), medical research has been puzzled by the fact that the etiology of most common diseases depends not only on discrete genetic and environmental causes but also on the interaction between the two. Separate estimates on the contributions of genes and the environment to a disease without considering their interactions will only incorrectly describe the proportion of the disease (i.e., the population attributable risk) that is explained by genes, the environment, and their joint effects (Figure 5). A landmark discovery in this respect was the finding that the association of a polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*, commonly known as 5-HTT) with depression is influenced by stressful life events (131). Following on the concept of gene-environment interaction has been increasingly applied to quantitative epidemiological studies, although the nature of the mechanism(s) underpinning such interplay remained so far elusive. Two recent studies on gene-environment interactions in PTSD shed light on the potential contribution of epigenetic mechanisms as a mediator between risk alleles and early life events.

The neuropeptide PACAP (pituitary adenylate cyclase activating polypeptide) binds to the G-protein coupled receptor PAC1 (132) and is involved in the brain's response to stress. The PAC1 protein is encoded by the gene *ADCYAP1R1* that has been recently suggested to influence in a sex-specific manner whether an individual will develop PTSD (133). A cohort of urban primary-care patients who had been exposed to severe trauma (child maltreatment, a serious accident or attack with a weapon) showed a positive correlation between peripheral blood levels of PACAP and the extent of posttraumatic stress syndromes, but only in women. High PACAP values correlated with physiological measures of the acoustic startle reflex which has been previously associated with PTSD. Moreover, in a translational animal model the mRNA expression of PAC1 was increased in the amygdala of adult mice following classical fear conditioning and as a function of estrogen exposure.

Notably, a common genetic variant (rs267735) in *ADCYAP1R1* associated with PTSD. This finding was replicated in a second cohort of patients exposed to trauma, once again only in women (133). Differential DNA methylation of *ADCYAP1R1* associated

with PTSD symptoms and included the variant rs267735 which maps to a predicted estrogen response element. In support of a regulatory role of this genetic variant, postmortem analysis of female brains evidenced differential expression of PAC1 mRNA as function of the underlying genotype.

Together, these findings offer insight into the question of why women are more likely than men to develop PTSD and suggest that traumatic stress can leave an enduring memory trace on the epigenome by DNA methylation at regulatory polymorphic sites of genes that participate in the stress response. The regulatory site at *ADCYAP1R1* maps to an ERE which undergoes DNA methylation in response to early trauma and thus constitutes an epigenetic risk factor for the later development of PTSD in women.

Similarly, a recent study suggested that a polymorphism in the FK506 binding protein 5 gene (*FKBP5*) can serve as a substrate for early trauma-dependent epigenetic marking to increase the risk for PTSD (134). *FKBP5* controls GR function by reducing ligand binding and translocation of the receptor complex to the nucleus (135). Hereby, *FKBP5* forms part of a negative, intracellular, ultra-short feedback loop due to GR-dependent transactivation at a glucocorticoid response element (GRE) situated in intron 2. A polymorphism identified in this intron gave rise to a potential TATA element supporting the assembly of the transcriptional machinery. Adults who were homozygous or heterozygous for the A (risk) allele at this polymorphism rather than the G (protective) allele were more likely to suffer from PTSD – provided they had experienced abuse as children. The risk allele conferred an altered chromatin structure and increased transcription of *FKBP5*, hence strengthening the negative feedback loop that attenuated GR activity. Impaired GR function, in turn increases the hormonal response to stress.

How do traumatic experiences then act together with the risk allele in PTSD? Traumatic experiences lead to activation of the GR which is known to initiate changes in DNA methylation (136). Notably, CpG residues in intron 7 of *FKBP5* – flanking a predicted GRE – were less methylated in risk allele carriers with a history of childhood abuse compared to those without a history of early trauma or traumatized patients without the risk allele.

In a translational *in vitro* model of early-life stress, treatment of hippocampal progenitor cells with dexamethasone elicited demethylation of intron 7 during proliferation and differentiation. The decline in methylation persisted over 20 days in steroid-free culture compatible with the idea of an enduring epigenetic mark. Furthermore, demethylation in intron 7 of *FKBP5* increased *FKBP5* expression, GR resistance, and led to corresponding changes in the expression of downstream genes in PTSD patients harboring the risk allele. In contrast, risk carriers exposed to trauma in adulthood showed maintained DNA methylation at intron 7 suggesting that epigenetic programming of *FKBP5* is confined to a critical time window of hippocampal cell development. Compatible with this view, demethylation at intron 7 in hippocampal neuronal progenitor cells occurred only during the proliferative phase (134).

Consistent with the role of glucocorticoids in controlling *Fkbp5* expression via DNA methylation, treatment of adolescent mice with corticosterone across 4 weeks enhanced gene expression in

the hippocampus, hypothalamus, and peripheral blood cells (137, 138). This was accompanied by demethylation at intron 5 and 1 in brain tissues and peripheral blood cells, respectively. Interestingly, either intron includes a GRE binding site. Moreover, treatment doses correlated with *Fkbp5* expression and demethylation at intron 1 indicating that intron 1 demethylation could serve as a biomarker for prior glucocorticoid load (138).

Together, these findings support the concept that exposure of children carrying the risk allele to stress can elicit enduring epigenetic changes in *FKBP5* gene expression predisposing them to stress-associated disorders such as PTSD (Figure 5).

CONCLUSION

More than 100 years have passed since Sigmund Freud described the influence of early traumatic experiences on later mental health. Numerous epidemiological, clinical, and translational studies have corroborated the powerful role of early life adversity for the development of depression and PTSD. During sensitive windows of development, adversity can lead to enduring (mal-) programming of the stress system which constitutes an important risk factor for later disease.

Epigenetic mechanisms mediate the dialog between our genes and the environment and can elicit lasting changes in gene expression potential. Experience-dependent epigenetic programming of stress genes is increasingly recognized as an important pathway in the deregulation of stress systems in rodents and patients. Such programming can confer an enhanced risk on disease development upon re-exposure to trauma or stress (Figure 5). Epigenetic programming is, however, not deterministic. In translational models, an enriched environment can attenuate the effects of epigenetic programming. Epigenetic modifications appear amenable across all chapters in one's life and thus offer great opportunities for timely interventions comprising pharmaceutical and psychotherapeutic treatments.

Nearly twice as much women are affected by stress-related mood disorders compared to men. The HPA axis, the central mediator of the stress response, shows clear sex differences which seem to impact on the prevalence and course of stress-related diseases. Further clinical and translational studies focusing on sex differences in epigenetic programming of HPA-axis activity and brain functions in response to traumatic and social experiences can advance our insight into the sex-bias of PTSD and depression. Epigenetic biomarkers (i.e., *GR* and *FKBP5* in PBMS) in populations at risks appear promising to inform about previous stress exposure and require further clinical investigations.

With the decoding of the human genome at the turn of the millenium, medical research pinned its hope, above all, on the identification of gene variants coming along with an elevated risk of contracting a disease (Figure 5). However, it has become clear that genetic factors and environmental influences are not independent of each other and that acquired pieces of information deliver the instruction how to interpret the genetic blueprint. Whether or not a genetic predisposition manifests as PTSD or depression then seems to depend on how genes and environment conspire. Epigenetic programming in response to trauma or stress can be modified by genetic variation in the underlying substrates. Hereby, silent variations are switched into epigenetic risk

factors for PTSD or depression in response to additional adversities (Figure 5). Further studies are needed to address tissue-specificity of experience-dependent programming of genetic variants to distinguish between roles as biomarker, reflecting humoral changes in response to trauma versus roles as epigenetic risk factor driving disease development.

Taken together, epigenetic mechanisms play an important role in experience-dependent programming of stress genes and their genetic variants. Moreover, epigenetic biomarkers encoding previous trauma and stress history might guide early therapeutic interventions and risk management in PTSD and depression on a long-term perspective.

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- Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Received: 29 April 2013; accepted: 22 July 2013; published online: 07 August 2013.
Citation: Raabe FJ and Spengler D (2013) Epigenetic risk factors in PTSD and depression. *Front. Psychiatry* 4:80. doi: 10.3389/fpsyt.2013.00080
- This article was submitted to *Frontiers in Molecular Psychiatry*, a specialty of *Frontiers in Psychiatry*.
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